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Low birth weight – the less than 2500g cut-off: is it applicable to Sri Lanka?

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Chief guest Honorable Yasantha Kodagoda, guest of honor Professor Mike Robson, President, Members of the Council, Past presidents, Life member of the Perinatal Society of Sri Lanka, Distinguished Invitees, Ladies and Gentlemen. I consider this as an honour and privilege to be able to deliver this year's Perinatal Society of Sri Lanka oration and I thank the President and the Council for giving me this opportunity.

Introduction

Low birth weight is defined as babies with a birth weight of less than(<) 2500g by the World Health organization. This 2500g cut appears to have been linked with 20 times higher mortality in this birth weight category, compared to those who were heavier at birth[1]. However, we now know that reduction in birth weight is the result of either prematurity or fetal growth restriction, and that mortality is directly linked to the severity of prematurity or the severity of growth restriction, rather than having an independent relationship with birth weight itself[2]. Categorization of mortality according to low-birth-weight infants was first reported by the French obstetrician Pierre Budin (1864-1908), in 1898 as 95% for birth weight <1200g, 85% for birth weight between 1200-1499g, 61% for birth weight between 1500-1999g and 33% for birthweight > 2000g[3]. John Ballantyne, a Scottish physician and obstetrician was the first to describe prematurity, as those between a birth weight between 3.5 – 4lbs (1590g-1810g) with a mortality of 50% and morbidity of 100%[4].

The origin of the 2500g cut off for birth weight appears to have been from the work done by Prof. Aravo Henrik Ylppo (1887 – 1992), also known as the Finnish father of Paediatrics, who was the first to replace the term 'congenital weaklings' with 'premature infants', introduced the concept for birth weight and length for gestational age and formulated the first preterm growth curves[5]. A study conducted in 1921 that acknowledged that the low birth weight cut off at <2500g was arbitrary, reported that mortality was 10 times higher in this category with a birth weight <2500g[2]. In 1935, this cutoff was codified by the American Academy of Paediatrics, that defined prematurity as birth weight ≤ 2500g[2]. In 1948, the First World Health Assembly adopted this as the global standard, following the recommendation of the World Health Organisation (WHO) Expert group on Prematurity who defined prematurity as birth weight ≤ 2500g or "immature" or <37 weeks gestation[2].

Awareness of the limitations in using birthweight to define prematurity was seen in the 1950s, where differences between aetiologies were described for prematurity and low birthweight. In 1955, Schlesinger and Allaway clearly stated that birth weight was a poor indicator of prematurity although it was easier to measure than gestational age and demonstrated that mortality was decreased within the higher weight (<2500g) and higher gestational age

(<36weeks) categories[6]. Improvement of the quality of data demonstrated the association between higher neonatal mortality and morbidity in infants with lower birth weight and earlier gestational ages[7-14]. Increase in the understanding of the differences between low birth weight, prematurity and small for gestational age (SGA) led to the AAP proposing nomenclature to characterize SGA in 1966[15,16].

Increase in knowledge on the effect of population characteristics (ethnicity, geographical location and socioeconomic status) that modified the relationship between birth weight and adverse birth outcomes, led to questioning of the appropriateness of the universal birth weight cutoff [9-10,17-250]. Modeling of birth weight was used to determine the morbidity and mortality risk within and between populations[18]. Following comprehension that birth weight differed between populations, Rooth described that the universal cutoff of 2500g was inadequate and proposed a cutoff of birth weight less than 2 standard deviations below the local population mean[23].

Studies done in the 1950s questioned the relationship between prematurity and low birth weight where higher mortality was associated with lower gestational age rather than being based on birth weight alone[6,7]. This led to the first description of 'small for gestational age (SGA)' by the AAP in 1966[8], which evolved in to its current definition, as birth weight below the 10th centile or – 2 standard deviations (-2SD) below the reference population in the 1990s[9-11]. Meanwhile research done in 1970s described how birth weight was affected by different characteristics of the population, such as the sex, ethnicity, geographical location and socio economic status[12-16]. This led to the understanding that an universal cutoff of 2500g may not be appropriate, due to difference in birth weight among different populations, leading Rooth to propose the use of a birth weight that was less than 2 standard deviations below the local population mean in 1980[23]. The WHO was also seen to question the validity of the 2500g cut off in 2004, due to the occurrence of high incidence of low birth weight without a high neonatal mortality in Sri Lanka[30]. In 2012, antenatal ultrasound scan was noted to be a more reliable predictor of morbidly and mortality as it helped to differentiate between prematurity and small for gestational age. This led to the WHO stating that reliance on the 2500g cutoff as a predictor of morbidity and mortality should be limited to settings that are unable to determine gestational age[31]. The usefulness of the 2500g cutoff is obsolete In Sri Lanka, where early antenatal ultrasound between 8-13 weeks of gestation is standard of care. However, a population specific cutoff for SGA at term gestation would help to identify the SGA babies that need monitoring in the postnatal ward.

This brings us to question if the 2500g cut off represented SGA in the WHO child growth standard (WHO-CGS). Interestingly, the birth weight of 2500g coincided only with the 3rd centile for boys in the WHO-CGS and was only suitable as a cutoff for SGA at term gestation only for boys. The 3rd centile for girls in the WHO-CGS was 2400g, being different from the 2500g cutoff [32,33]. The next question is, whether WHO-CGS represents the growth of healthy children in Sri Lanka? A review done across 55 countries by Natale et al. found difference in weight, height and head circumference in >20% from the WHO-CGS where the means of European countries were consistent outliers above the mean in contrast to the means of developing countries that were consistently below the mean[34]. Cross sectional data from Gampaha and Kandy districts in Sri Lanka, also supported these findings, where the birth weight, length and head circumference were found to be significantly lower than the WHO-CGS[35,36]. However, WHO-CGS growth data from birth to 2 years were

obtained from longitudinal data using the LMS method[37]. This highlighted the need for a longitudinal study on healthy Sri Lankan children with methodology comparable to the WHO-MGRS.

This led us to undertaking the first longitudinal study on anthropometry, body composition, infant development and IYCF practices from birth to 2 years in Sri Lanka as well as in South Asia. This study also formed the Sri Lankan component of the first global longitudinal body composition study which also included Australia, Brazil, India, Pakistan and South Africa and was funded by the International Atomic Energy Agency of which the findings were published not only. In the American Journal of Clinical Nutrition but also in the European Journal of Clinical Nutrition. This is the first study that has comprehensively described longitudinal changes in growth within the first 2 years of life (anthropometry, growth velocity and body composition) in a study population, which had very high adherence to IYCF and with similar methodology to WHO – MGRS, in addition to describing the factors affecting body composition (birth weight, infant feeding, placental factors and cord blood insulin, leptin, adiponectin and IGF-1), as well as the effect of body composition, on infant development.

Methodology

We conducted a descriptive, longitudinal, cohort study at the University of the De Soysa Hospital for Women, Sri Lanka from 0.1.07.2015 to 31.12.2019.

All pregnant women admitted to the university obstetric ward at a period of gestation from 37 to 41+6 weeks i.e., term gestation, were screened twice daily on all weekdays. All healthy babies born to women admitted to the University obstetric wards at term gestation, with a singleton pregnancy, aged over 18 years, living in the Colombo district, who were not smoking and had an intention to breastfeed with an income above 1st quintile according to the 2006/2007 census data and agreed to attend follow up one-monthly during the first year and two-monthly during the second year were included in the study. Women who did not fulfil the inclusion criteria were excluded from the study. Infants with congenital abnormalities, disease conditions affecting growth, illness requiring hospital admission or an Apgar score < 8 at 5 minutes were excluded from the study.

This study was funded by the International Atomic Energy Agency (IAEA). Sample size was calculated as 150 with a power of 90% to detect differences in FM and FFM among males and females at 2 years of age[36]. Ethics approval was obtained from the Faculty of Medicine, University of Colombo (EC-14-145).

Data was collected using interviewer administered questionnaires and data recording forms. English questionnaires were translated and back translated into Sinhala and Tamil and was pretested on 25 infants. Questionnaires were administered in the language of the parent's choice where separate questionnaires were used for screening and birth anthropometry, parental information, infant follow up, 24-hour dietary re call and food frequency.

Period of gestation (POG) was assessed using crown rump length measured via antenatal ultrasound scan done between 8-13 weeks of period of amenorrhea as per national standard. In case of unavailability, biparietal diameter measured by antenatal ultrasound done between 13-20 weeks was used. Last regular menstrual period of the mother was used to assess POG when both these options were not available.

Anthropometry was performed by me in all study participants following training and certification by an International Society for the Advancement of Kinanthropometry (ISAK) Level 2 accredited anthropometrist

according to WHO-MGRS protocol. Second measurements were performed by research assistants trained by me. Father's anthropometry and mother's height were measured at recruitment while the mother's pre pregnancy weight was obtained from the pregnancy record. Measurements at birth were made within the first **12-24** hours. Measurements of weight, length, circumferences (chest, abdomen, mid arm, head) and skinfold thickness (biceps, triceps, subscapular and supra iliac) in the infant, parents' weight and height were measured to the nearest 5g, 1mm, 1mm and 0.2 mm, 100g and 0.1cm respectively. All measurements were done using Seca GmbH instruments except for the Harpenden skinfold caliper according to the WHO-MGRS protocol. Instruments were calibrated twice weekly. This study adopted the same quality control methods for anthropometry as used in INTERGROWTH-21, with weekly calibration of instruments and 6 monthly standardization. Technical error of mean was at the level of skilled anthropometrist for both first and second intra observer measurements[38].

Placental weight was measured using the same instruments to the nearest 5g whereas the maximal diameter and maximal thickness were measured using a stainless-steel ruler.

Dietary data was collected using 24-hour dietary recall, food frequency and interviewer administered questionnaires. Individual dietary counselling was done regarding the dietary components, consistency, timing of meals / water / breastfeeds, mealtime behaviour and interpretation of the growth curves. A mutually agreed plan was documented in the infants clinic book in the preferred language at each visit and was followed up by myself. All participants parents were given access to a 24-hour hotline to obtain advice regarding diet / breastfeeding. IYCF practices of the study participants were assessed using 2021 UNICEF/WHO guidelines and the 2007 Sri Lankan Ministry of Health guideline[39-40].

Body composition is what we are made of and can be described according to the 2-compartment model, where the body is described as fat and fat free mass. Higher compartment models describe the sub components of the fat free mass. Body composition was assessed using the deuterium, which is a naturally occurring stable isotope of hydrogen. The dilution principle was used to assess body composition after the administration of deuterium oxide. Deuterium oxide (D, 99.9%) was administered at 0.1g/kg at 3,6,9,12,18 and 24 months. Administered dose was calculated by determining the difference in weight between the pre and post administration weights of the syringe containing the dose using a 5 stage Shimadzu analytical balance. Saliva samples were obtained using cotton swabs in to screw capped NUNC vials prior to dosing as well as 2.5 and 3 hours after dosing and was stored at -20C. Concentration of deuterium oxide in saliva was measured using Agilent Fourier Transform Intra Red (FTIR) spectroscopy using micro lab software. Multiple methods including daily diagnostics, testing samples in duplicate and excluding samples with total body water percentage outside the range of 40-75% were used to ensure strict quality control[41]. Total body water was calculated using the dilution principle. Fat free mass (FFM) was calculated using Fomon's age and sex specific hydration factors[42]. Fat mass (FM) was calculated by subtracting FFM from the body weight. Fat mass index(FMI) was calculated by dividing the fat mass (kg) by the length (cm) whereas fat percentage (Fat %) was calculated by dividing the FM by the body weight.

Enzyme Linked Immuno Sorbent Assay (ELISA) was conducted for leptin, adiponectin, insulin and IGF-1 in cord blood (10ml) that was collected at the time of birth and stored at -80C after centrifuging. DRG

Leptin Sandwich ELISA EIA-2395 (DRG Instrument GmBH, Germany), DRG Insulin Sandwich ELISA EIA 2935 (DRG Instrument GmBH, Germany), Demeditec Adiponectin ELISA DEE009 (Demeditec Diagnostics GmBH, Germany) and Demeditec IGF-1 600 ELISA kit DE4140 (Demeditec Diagnostics GmBH, Germany) were used to measure leptin, insulin, adiponectin and IGF-1 respectively. Quality control was ensured via the use of control samples, Levey Jennings charts, monitoring intra and inter assay variation, running samples in duplicate with CV < 20% between duplicates and ensuring that sample results were within the assay range as specified by the manufacturer as well as within clinical range.

I also conducted Bayley III assessments on all participants at 3,6,9,12,18 and 24 months in the family's language of choice using the unmodified tool, where raw scores were recorded for all domains. Scaled scores and growth scores were derived from raw scores, whereas composite scores were derived from scaled scores.

Statistical analysis was done using SPSS version 27 for Mac. Data cleaning was performed using box and whisker plots for cross sectional data and 'plot clean' and 'velout' functions using Sitar on R studio. Normality of the distribution was checked using the Shapiro Wilk test. Z scores were determined using the WHO anthro analyser for MacBook. Longitudinal curves and percentiles were determined via LMS chart maker. Relationships between variables were determined using the independent sample T test, Pearson and Spearman correlation and simple, multiple and hierarchical linear regression after satisfying all assumptions. Age at each visit was calculated using the visit date and the date of birth. A 30-day period was taken as a month.

Results

The total screened were 4140, of which only 877 were eligible, of which only 427 consented and were recruited prior to delivery, of which only 344 consented after delivery. Seven babies were excluded due to birth records not being available resulting in a study population of 337 at birth. Study population was 157, 122, 76, 44 and 36 at 1,3,6,12,18 and 24 months of age. The main reason for the dropouts were that many parents moved out of the study area to their grandparents' place of residence for extended family support and found it difficult to attend the clinic visits. None of the children who attended follow up visits were found to have any disease condition affecting growth or requiring hospital admission.

Comparison of socio demographic data of our Sri Lankan study population with the WHO MGRS revealed many similarities between the two groups, such as the number of live births,, proportion of families with children younger than 3 years, parity, maternal age and ownership of commodities such as piped water, flush toilet, refrigerator, gas / electric cooker, telephone and vehicle apart from significantly lower parental height and median monthly income in our Sri Lankan study group[43]. In contrast, our Sri Lankan study population showed a significantly higher adherence to IYCF guidelines, especially breastfeeding, where initiation of breastfeeding was 100% vs 65.7%, exclusive breastfeeding within the first 4 months was 97.8% vs 74.7%, breastfeeding at 12 months was 99% vs 68.3%, initiation of complementary feeding by 6 months was 100% vs 99.5% and age of initiation of complementary feeding was 5.5 $\pm$ 1 vs 4.9 $\pm$ 3.5 months in our Sri Lankan study population and WHO-MGRS respectively.

Comparison of birth anthropometry revealed that our Sri Lankan study population showed a left shift of 0.6 – 0.9

compared to the WHO-MGRS, with lower z scores for length for age, weight for age and weight for length by 0.6-0.9[43]. Same 0.6-0.9 left shift was noted in the z scores from birth to 2 years in our study population, despite the higher adherence to the IYCF guidelines in our study population compared to WHO MGRS. This resulted in weight for age, length for age and weight for length < -1SD being falsely labelled as underweight, stunting and wasting with the use of WHO-CGS, highlighting the need for country specific growth references [44].

Using the longitudinal growth curves we developed for our healthy Sri Lankan population, it was noted that the 3rd centile for weight for age at birth, i.e., the -2SD cut off, signifying the cut off for small for gestational age (SGA) at term gestation, was at a birth weight of 2.2 kg, for both boys and girls.

Next let's have a look at the biological evidence to determine whether the birth weight of 2.2 kg as determined by the -2SD cut off based on our population specific longitudinal growth curves is a better indicator of SGA at term gestation that the low birth cut off at 2.5 kg.

SGA is associated with higher FM, obesity and non communicable disease (NCD) [45,46]. Therefore, body composition was compared at 3, 6, 9, 12 and 24 months of age between babies with a birth weight that was appropriate for gestational age (AGA) with that of SGA. SGA was taken as < 2.5kg as per current low birth weight cut off in the first comparison, whereas SGA was taken as < 2.2kg as per proposed cut off for SGA determined by the population specific growth references developed in this study in the second comparison. When 2.5kg was taken as the cut off for term SGA, there was no significant difference in the fat mass indicators between SGA and AGA although FMI and Fat % were found to be marginally higher in SGA vs AGA at 6, 9 and 24 months of age. In contrast, when 2.2 kg was taken as the cut off for SGA, all fat mass indicators i.e., FM, FMI and Fat % were higher in SGA compared to AGA with significant differences ($p<0.05$) in all parameters at 6 and 9 months of age. So, is 2.2kg better than 2.5kg in demonstrating a higher fat mass leading to future risk of non-communicable disease (NCD) in term SGA? The answer is clearly, yes.

Let's have a look at the placenta and see if we can find supportive evidence to corroborate the changes in body composition detected by the deuterium dilution method.

This is the first study to describe placental thickness being related to infant body composition, where increase in placental thickness was associated with an increase in fat % at 18 months of age[47]. In addition, the ability of under nourished fetuses with certain genotypes to expand the placental surface to obtain more nutrients have also been described by Erikson et al[48]. Comparison of placental parameters using the 2.5 kg cut off revealed, that the placentas of SGA babies had a significantly lower ($p<0.05$) weight and diameter with sparing of the placental thickness. In contrast, the use of the 2.2kg cut off revealed, that the placentas of SGA babies had a significantly lower ($p<0.05$) weight with sparing of the placental thickness as well as its diameter. An SGA baby would be expected to have a smaller placenta with lower weight, diameter as well as thickness, where all parameters are expected to be significantly smaller compared to AGA. Not finding a significant difference between some of the placental parameters indicate that these parameters may have an active role in the SGA baby, where increase in diameter may have a role in increasing the surface area and increase in thickness is related to the body composition resulting in increased fat mass at 18 months of age. While the 2.5 kg cut off demonstrated sparing of the placental thickness, the 2.2 kg cut off demonstrated sparing of both the placental diameter as

well as the placental thickness. Therefore, is <2.2kg better than <2.5kg in demonstrating placental characteristics in term SGA? The answer is of course, yes.

Now, let's have a look at the adipokines and growth factors in the cord blood. Our study revealed that insulin was associated with an increase in FM at 24 months of age, IGF-1 with an increase in FFM at 9 months of age, adiponectin with the healthy body composition pattern of the breastfed baby in contrast to leptin which was not associated with body composition from 3-24 months of age[49]. These findings were agreement with previous research findings[50-54]. Comparison of cord blood adipokines and growth factors between SGA and AGA revealed that SGA babies had a significantly lower ($p<0.05$) level of leptin and IGF-1 level with the 2.5 kg cut off compared to a significantly lower ($p<0.05$) level of leptin, IGF-1 and insulin with the 2.2 kg cut off. The difference in insulin was detected only with the 2.2kg cut off, whereas the difference in leptin and IGF-1 was detected with both cut offs. A systematic review and meta-analysis done by Manapurath et al. also revealed that SGA was associated with a significantly lower level of insulin, leptin and IGF-1 in agreement with our study findings, while also indicating that SGA babies are born with lower levels of FM as well as FFM[55]. Is <2.2kg better than <2.5kg in demonstrating cord blood factors in term SGA? The answer is, yes again.

SGA babies are described to have catch up growth mainly due to an increase in fat mass[46]. Our study found that abdominal circumference and skinfold thickness showed the highest correlation with FM compared to weight, length and circumferences of head, chest and arm. Our study findings agreed with that of previous researchers[56-57]. Comparison of weight for age, length for age, abdominal circumference for age and subscapular skinfold thickness for age charts between SGA and AGA using the 2.5 kg and 2.2 kg cut offs demonstrated that catch up growth was demonstrated only with the 2.2kg cut off. So, is <2.2kg better than <2.5kg in demonstrating anthropometric changes depicting catch up growth in term SGA? And of course, it's yes again.

Comparison of Bayley III scores at between SGA, AGA and LGA babies at term gestation at 3, 6, 9, 12, 18 and 24 months of age, using the 2.5 kg and 2.2 kg birth weight cut offs revealed that there was no significant difference in Bayley III scores with the 2.5kg cut off. However, the use of the 2.2 kg cut off demonstrated lowest scores ($p<0.05$) in SGA babies for self-direction at 3 months of age, expressive language at 6 months of age and fine and gross motor at 9 months of age. However, the disappearance of these differences at 12,18 and 24 months of age is likely due to the optimal nutrition and stimulation given to hese babies**.** Is <2.2kg better than <2.5kg in demonstrating changes in infant development in term SGA? And again, it is yes.

In summary, weight, length and weight for length in healthy children were 0.6 – 0.9 SD lower than WHO-MGRS despite > 90% high adherence to IYCF, implying that WHO-CGS is not appropriate to identify term SGA for Sri Lankan infants. The population specific cutoff at -2SD (3rd centile) for term SGA was 2.2kg according our longitudinal growth curves from birth to 2 years. Changes typical of SGA were better demonstrated with the <2.2 kg than < 2.5 kg with regard to infant development, body composition, anthropometry, placental size as well as cord adipokines and growth factors.

What are the implications for practice?

Use of the <2.5kg cutoff incorrectly diagnose 'normal' Sri Lankan children as term SGA, classify them as high risk, increase burden on health sector and force

catch up growth, increasing the risk of obesity and metabolic syndrome.

What is the burden on the health sector with <2.5 kg cutoff?

Using the 2.5 kg cut off instead of the 2.2kg cut off results in an increased hospital stay, increased burden on nursing care and increased capillary blood sugar monitoring for a minimum of 48 hours, in addition increased multivitamin and iron supplementation and an increased burden on clinic follow up during the first 2 years of life.

Mislabeling SGA with <2.5 kg cutoff, increase parental and midwife anxiety, who in turn attempt to achieve catch up growth and move child's weight from the "orange" / "red" zone into the "green" zone at any cost, resulting in force feeding, and commencing unhealthy foods with sugar and salt as well as formula feeds, which in turn increases the risk of obesity and NCD.

Problems identified included that the WHO-CGS was unsuitable for growth interpretation from birth to 2 years in SL, that the 2.5kg birthweight is not suitable to identify high risk babies at term gestation, trying to push up SGA to 'green' zone in the CHDR and undue parental anxiety caused by the CHDR color scheme and terminology.

Proposed solutions include, the use of population specific growth charts for growth interpretation, as well as the use of population specific -2SD to identify term SGA, i.e., to use <2.2 kg, instead of <2.5 kg, to strengthen awareness programs among the public and health care workers that babies should grow along their birth centile and that trying to push SGA to the "green zone" or above their birth trajectory will increase their risk of obesity and its complications, to use similar colors or remove colors and advocate for growth along the birth trajectory and to remove the alarming terminology used to describe -1SD, -2SD and -3SD.

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